

AD_____

AWARD NUMBER: W81XWH-14-1-0598

TITLE: Use of a Portable Stimulator to Treat GWI

PRINCIPAL INVESTIGATOR: Jorge M. Serrador, PhD

CONTRACTING ORGANIZATION: Veterans Biomedical Research Institute
East Orange, NJ 07018

REPORT DATE: October 2016

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE October 2016		2. REPORT TYPE Annual Report		3. DATES COVERED (From - To) 30 Sep 2015 - 29 Sep 2016	
4. TITLE AND SUBTITLE Use of a Portable Stimulator to Treat GWI				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-14-1-0598	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Jorge M. Serrador, PhD Kelly Brewer, MS				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Veterans Biomedical Research Institute 385 Tremont Ave East Orange, NJ 07018				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT The purpose of this research is to characterize vestibular function in a population of veterans with Gulf War Illness and determine if subsensory electrical stimulation can improve vestibular function. To date, we have collected vestibular screening data on nine subjects, with four scheduled to return for visits using electrical stimulation. Since we have preliminary data only and have not completed subject visits using electrical stimulation, we are unable to report any significant finding during this research period.					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF: U			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 13	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER (include area code)

TABLE OF CONTENTS

	<u>Page No.</u>
INTRODUCTION	4
KEYWORDS	4
ACCOMPLISHMENTS	4
IMPACT	9
CHANGES/PROBLEMS	9
PRODUCTS	11
PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS	12
SPECIAL REPORTING REQUIREMENTS	13
APPENDICES	13

1. INTRODUCTION

Gulf War Veterans have a significantly greater incidence of reporting dizziness, suggesting vestibular involvement. Gulf War Veterans with Gulf War Illness (GWI) demonstrate impaired balance, specifically during conditions which rely on vestibular inputs, suggesting vestibular impairment in ~50% of this population. In this study, we will determine the level of vestibular dysfunction within Veterans with GWI and apply the novel method of stochastic noise, shown to improve neural signals, to enhance vestibular function and balance in those with vestibular impairments. To treat Veterans diagnosed with GWI that have vestibular (balance) dysfunction we will use a portable stochastic noise electrical stimulator that provides low levels of stimulation which is imperceptible to enhance vestibular and balance function.

2. KEYWORDS

Vestibular, Gulf War Illness

3. ACCOMPLISHMENTS

MAJOR GOALS OF THE PROJECT

Major Goal 1 – Characterize vestibular dysfunction in Veterans with Gulf War Illness

Subtask 1: Establish Project Management System/Develop Logistical Plan (Sept- Dec 2014)

- a. Train the current members of the team (research assistant) on vestibular screenings, balance assessments, galvanic stimulation (**completed**)

Milestone #1: Establish project management system, hire and train research staff (Planned Completion Dec 2014) – **100% complete**

Subtask 2: Regulatory Review and Approval Process (Sept - Dec 2014)

- a. Finalize IRB paperwork including application, protocol and consent form (**completed**)
- b. Submit any revisions requested by the regulatory board prior to approval (**completed**)
- c. Obtain DoD HRPO approval (**completed**)

Milestone #2: Regulatory review and approval obtained (Planned completion Dec 2014) – **100% complete**

Subtask 3: Recruitment Plan (Sept 2014 – June 2015)

- a. Develop plan to meet recruitment goals (**completed**)
 - b. Mail IRB approved recruitment letters to Veterans seen at the WRIISC; follow up with phone calls
 - ~150 Gulf War Veterans evaluated at the WRIISC– 25 letters per week will be mailed to this subset followed by a phone call
- (We have attempted to contact 267 Veterans. Of the 176 veterans that have been**

- contacted by phone to participate in the study, 110 were interested in participating and screened for the study and 51 are eligible for study visits)**
- c. Distribute flyers to all VA facilities and their ambulatory services including community-based outpatient clinics to publicize the study
 - d. Contact Veteran Service Organizations for support on best way to perform outreach **(having monthly meetings with VSO representatives that are Gulf War Veterans to discuss recruitment goals) (completed)**

Milestone #3: Recruitment Plan Executed (Planned Completion June 2015) -85% complete

Subtask 4: Determine the prevalence of vestibular impairment in GWI veterans (Aim 1) & Determine the effectiveness of subsensory electrical stimulation in a population of Veterans with vestibular dysfunction to improve balance function (Aim 2) (Dec 2014- June 2016)

- a. Screen subjects/ collect data: total of 140 subjects

- 3 subjects per week/ 3 study visits
- Vestibular testing, balance assessments

(35 subjects have been enrolled in the study)

Data analysis (Post-doctoral fellow/research assistant will continually analyze data as collected)

Aim 1:

-31 subjects have had their data analyzed

-Analysis shows 13 of 26 GWI subjects have otolith hypofunction (50%),

-Analysis shows 1 of 5 GW control subjects have otolith hypofunction (20%)

Aim 2:

-Of 31 subjects analyzed, 22 subjects are eligible to return for sub-sensory electrical stimulation in Aim 2 (71%) (both GWI and GW Control)

-18 of 22 subjects have completed study visits for Aim 2

-14 of 18 subjects have had their data analyzed, 4 are in process

-6 of 14 (43%) show improvement in OCR with electrical stimulation, including 5 of 12 (42%) GWI

Present/publish work

Milestone #4: Enrolled and tested subjects (Planned Completion March 2016) – 43% Completion

Milestone #5: Data analysis completed (Planned Completion April 2016) – 12% Completion

Milestone #6: Data presented/published (Planned Completion June 2016) –5% Completion (Talk given at 29th Barany Society meeting in Seoul, Korea, 2016 titled “Gulf War Illness in US Veterans is Associated with Otolith Hypofunction and Decreased Brain Blood Flow”)

ACCOMPLISHMENTS DURING THIS ANNUAL PERIOD

Major Activities

- Continued enrollment of study subjects
- Continued enrollment of controlled subjects with normal vestibular function to ensure that the stimulator does not have negative effects.
- Data analysis of enrolled subjects performed
- Continuing to bring subjects in for stimulation testing

Milestone #4: Enrolled and tested subjects (Planned Completion March 2016) – 43% Completion

Specific Objectives for Year 2

- 1) Continued execution of recruitment plan to screen subjects for enrollment
- 2) Continued enrollment and data collection
- 3) Analysis of data from enrolled subjects
- 4) Re-visit recruitment plans to further develop outreach events at VA NJ

Significant Results of Year 2

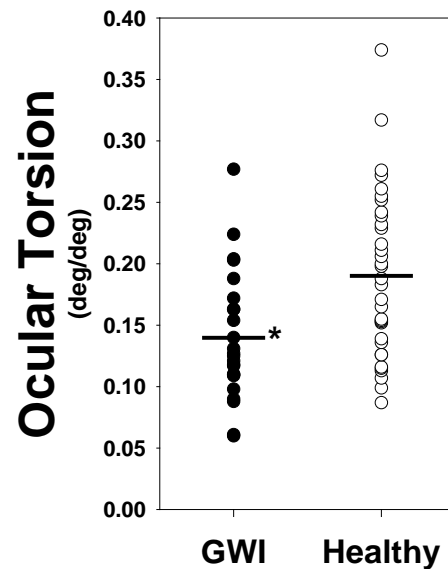
- 1) Phone calls have been made to 112 veterans within this past year resulting 51 phone screens to assess subject study eligibility.
- 2) Twenty-seven subjects contacted within this past year were eligible for initial study visit. Twenty-four subjects have been enrolled within this past year for a total of 35 subjects for the study.
- 3) Overall, 31 subject data has been analyzed with 22 eligible to return for sub-sensory electrical stimulation in Aim 2.

Major Findings, Developments, Conclusions, and Other Achievements

- We have three major findings to report so far:
 - 1) Veterans with Gulf War Illness show reduced ocular torsion indicative of otolith hypofunction
 - 2) Use of Stochastic Noise to stimulate the vestibular system did not produce a significant improvement in ocular torsion, unlike what we have seen in civilians and other veterans
 - 3) Despite a lack of improvement in ocular torsion, there was a significant improvement in balance, demonstrated by reduced mediolateral sway, however we didn't see the same effect in the anterior posterior sway.

Vestibular Hypofunction in Veterans with Gulf War Illness

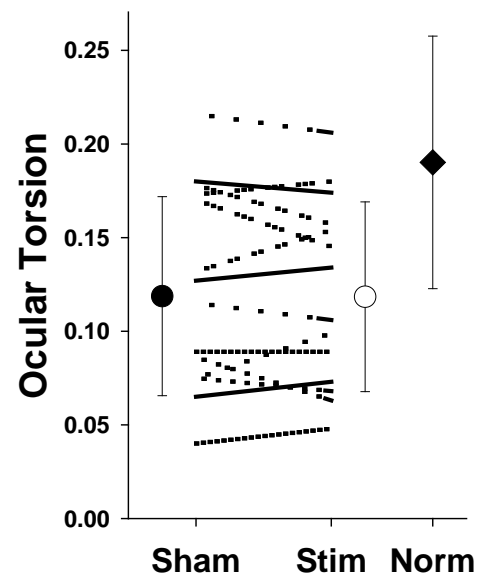
To determine if Veterans with Gulf War Illness have vestibular hypofunction we examined a group of GWI Veterans and found that they had significantly lower than an age and gender matched group of healthy civilians that Dr. Serrador had collected as part of a previous NASA research grant (Serrador et al, Neurosci Lett. 2009 Nov 6;465(1):10-5). The figure to the right shows the distribution of ocular torsion, a vestibular ocular reflex that is directly attribute to otolith function in both Veterans with GWI and healthy civilians. One can see that while there is a large distribution, the Veterans with GWI definitely have a distribution on the lower range and are showing significantly lower values than healthy individuals. This suggests that GWI is associated with otolith hypofunction. It remains unclear why this is occurring but the data suggest this is definitely the case.



Effect of Stochastic Noise Stimulation on Otolith Function

To determine if we could use subthreshold electrical noise to enhance vestibular function, we used the same low level electrical noise we had used previously in other veterans, and assessed whether this stimulation could increase ocular torsion. The figure to the right demonstrates that while it was able to improve ocular torsion in some veterans (~50%) it did not have a significant effect on ocular torsion in this group. This was quite surprising since we had previously found in veterans without GWI, that we were able to improve ocular torsion in ~90% of the participants. It remains unclear why we did not see the same level of improvement in the GWI group that we say in other veterans. We are currently trying to examine if GW era veterans without GWI show improvement similar to what we say in other veterans. Further work is needed to determine why the stimulus was not as effective in this group.

Effect of Stochastic Noise Galvanic Stimulation on VOR in Gulf War Veterans

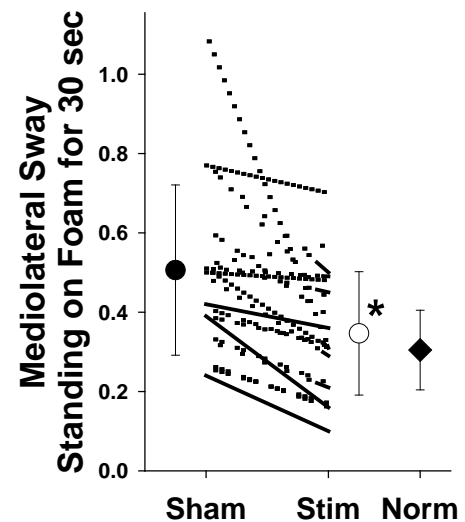


Effect of Stochastic Noise Stimulation on Static Balance Function

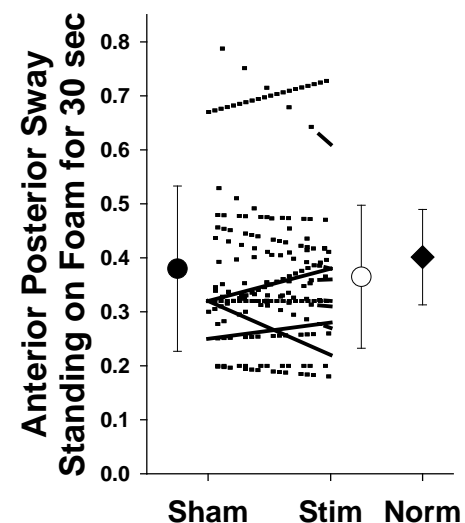
Our original hypothesis was that by improving vestibular function, i.e. ocular torsion, we would then also improve balance control. However, our finding that stochastic noise did not consistently improve ocular torsion made us skeptical that we would see a balance improvement. However, to our surprise, mediolateral sway while standing on an unstable surface consistently showed reduced sway during stimulation compared to sham. Interestingly there was not a similar improvement in anterior posterior sway. However, this finding was not unexpected since previous galvanic vestibular stimulation has shown that placement of electrodes over mastoid process results in greater affects on mediolateral sway. Thus our current electrode placement would most likely improve mediolateral sway. It is also interesting that the improvement occurred when veterans were standing on an unstable surface with eyes open. We did not see the improvement with eyes closed. We were expecting a greater improvement with eyes closed since when participants lack vision they must rely more heavily on the vestibular system. One possible explanation on why this didn't occur is that the increased vestibular inputs needed to be integrated with another sensory system such as vision to confirm their validity. Since we were only turning the stimulator on for brief periods the vestibular nuclei within the brain did not have sufficient time to adapt to the increased vestibular information. However, with the addition of visual information, there was improved sensory integration and thus improved balance.

These data suggest that the stimulator is able to improve balance even in those that do not show improvements in ocular torsion. It remains unclear if that because vestibular function is still improvement but we are unable to detect using ocular torsion or another mechanism is involved. Another important finding is that if the reason we see the improvement with eyes open is because increased vestibular inputs must be integrated, we would expect that longer term stimulator use would allow for better integration of the improved vestibular info centrally, and thus possibly even greater improvements in balance.

Improvement in Balance (Reduced Sway) in Gulf War Veterans During Stochastic Noise Stimulation



Balance in Gulf War Veterans During Stochastic Noise Stimulation



What opportunities for training and professional development has the project provided?

This project has provided training for all research staff to be competent at vestibular screenings, balance assessments, and electronic stimulation procedures. The staff have been able to travel to Dr. Schubert's clinic at Johns Hopkins to be trained on most up to date vestibular testing techniques.

How were the results disseminated to communities of interest?

- Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals?

- 1) Continued execution of recruitment plan to screen subjects for enrollment
- 2) Data collection and analysis from enrolled subjects
- 3) Re-visit recruitment plans to further develop outreach events at VA NJ

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?

- Nothing to Report

What was the impact on other disciplines?

- Nothing to Report

What was the impact on technology transfer?

- Nothing to Report

What was the impact on society beyond science and technology?

- Nothing to Report

5. CHANGES/PROBLEMS

- Nothing to Report

Changes in approach and reasons for change

- Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them

- Recruitment has been slower than expected, we have recruited 26 Veterans with GWI and 5 Veterans without GWI and we have 3 veterans with GWI currently scheduled to complete screening visit. We provided information to several veteran service organizations (Veterans of Foreign Wars, American Legion, Disabled American Veterans, National Gulf War Resource Center) about the research to recruit Veterans both locally and nationally. A majority of our recruitment efforts have been focused on a local population but we have increased our research efforts on a national to increase awareness and aid in our recruitment. We are currently working with Jim Bunker of the National Gulf War Resource Center to post an ad on the website that will highlight the study and the fact that travel funds are available to allow Veterans from anywhere in the nation to participate. We believe this will greatly increase the recruitment. When we had Mr. Bunker post a survey for to be completed by Gulf War Veterans in 2011, we had over 800 responses with 72 hours. We posted an advertisement to the VANJ Facebook page.
- We are still seeing a higher than expected rate of vestibular hypofunction within our population. After assessing 31 veterans with Gulf War Illness we see 50% with hypofunction. At our current rate, we would need to recruit 84 subjects to get to our desired 42 completed subjects. This will reduce the number required to screen and should assist in allowing us to complete the work as required.
- We obtained a no cost extension to allow us to recruit further veterans and complete our specific aims.

Changes that had a significant impact on expenditures

- There were no changes in expenditures.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents:

Significant changes in use or care of human subjects

- No changes to use of care of human subjects to report

Significant changes in use or care of vertebrate animals.

- No animal use research will be performed to complete the Statement of Work

Significant changes in use of biohazards and/or select agents

- No biohazards and/or select agents will be used to complete the Statement of Work

6. PRODUCTS

Publications, conference papers, and presentations

Journal publications.

- Nothing to Report

Books or other non-periodical, one-time publications

- Nothing to Report

Other publications, conference papers, and presentations.

Talk given at 29th Barany Society meeting in Seoul, Korea, 2016 titled “Gulf War Illness in US Veterans is Associated with Otolith Hypofunction and Decreased Brain Blood Flow”

Website(s) or other Internet site(s)

- Nothing to Report

Technologies or techniques

- Nothing to Report

Inventions, patent applications, and/or licenses

- Nothing to Report

Other Products

- Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Jorge Serrador, PhD

Project Role: PI

Nearest person month worked: 2.5

Contribution to Project: no change

Name: Bishoy Samy, MS

Project Role: Research Engineer

Nearest person month worked: 1

Contribution to Project: no change

Name: Tien Le, BEng

Project Role: Research Assistant

Nearest person month worked: 1

Contribution to Project: Has stopped work on project and taken new position

Name: Leslie De La Cruz, BS

Project Role: Research Assistant

Nearest person month worked: 3

Contribution to Project: Leslie has performed phone screens and recruitment of veterans including enrollment and data collection

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

- Nothing to Report

What other organizations were involved as partners?

1. Organization Name: University of Western Sydney- Paul Breen, PhD

Location of Organization: Australia

Partner's contribution to the project:

- Financial support – Nothing to report
- In-kind support – Dr. Breen's salary is covered by UWS as detailed in original proposal.
- Facilities – Nothing to report
- Collaboration – Designed a novel low power stochastic noise stimulator that will be used to improve vestibular function in our patients
- Personnel exchanges – Nothing to report
- Other – Nothing to report

2. Organization Name: Azusa Pacific University- Scott Wood, PhD

Location of Organization: California

Partner's contribution to the project:

- Financial support – Nothing to report
- In-kind support – Nothing to report
- Facilities – Nothing to report
- Collaboration – Provided expertise in scientific protocol development & vestibular assessment
- Personnel exchanges – Nothing to report
- Other – Nothing to report

2. Organization Name: Johns Hopkins University – Michael Schubert, PhD

Location of Organization: Maryland

Partner's contribution to the project:

- Financial support – Nothing to report
- In-kind support – Nothing to report
- Facilities – Nothing to report
- Collaboration – Provided expertise in scientific protocol development & vestibular assessment
- Personnel exchanges – Nothing to report
- Other – Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

- None

QUAD CHARTS: If applicable, the Quad Chart (available on <https://www.usamraa.army.mil>) should be updated and submitted with attachments.

9. APPENDICES: None.

Use of a Portable Stimulator to Treat Gulf War Illness

Innovative Treatment Evaluation Award

Funding Opportunity Number: W81XWH-14-1-0598



PI: Jorge M. Serrador, PhD

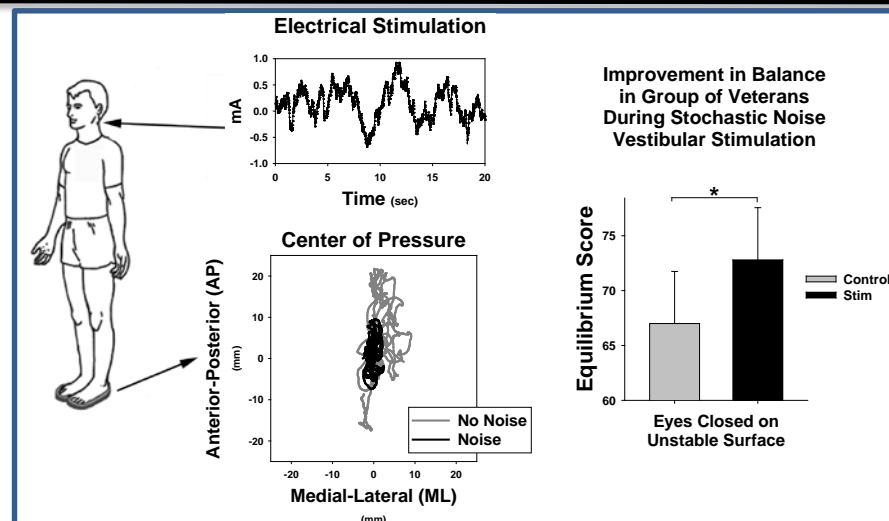
Org: Veterans Biomedical Research Institute Award Amount: \$553,095

Problem and Military Relevance

- Gulf War Veterans have a significantly greater incidence of reporting dizziness, suggesting vestibular involvement
- Gulf War Veterans with GWI demonstrate impaired balance, specifically during conditions which rely on vestibular inputs, suggesting vestibular impairment in ~50% of our sample
- We will determine the level of vestibular dysfunction and apply the novel method of stochastic noise, shown to improve neural signals, to enhance vestibular function and balance in those with vestibular impairments

Proposed Solution

To treat Veterans diagnosed with GWI that have vestibular (balance) dysfunction we will use a portable stochastic noise electrical stimulator that provides low levels of stimulation which is imperceptible to enhance vestibular and balance function



Left Panel: Sway data from a veteran during postural testing with eyes closed. Notice the significant reduction in both AP and ML sway with imperceptible stochastic noise electrical stimulation applied through skin electrodes just behind the ears.

Right Panel: Improvement in equilibrium in veterans during stochastic noise electrical stim.

Timeline and Total Cost

Activities	CY	14	15	16
Obtain Regulatory Review and Approval				
Execute recruitment plan to meet goals				
Vestibular screenings of GWI Veterans				
Sub-sensory galvanic stimulation testing				
Data Analysis				
Estimated Budget (\$K)		\$68.4	\$275	\$209.6

Updated: October 28, 2016

Goals/Milestones

CY14 Goal – Project Planning and Approval

- ☒ Establish Project Management System/Develop Logistical Plan
- ☒ Obtain Regulatory Review and Approval

CY14/15 Goals – Execute recruitment plan

- ☒ Develop and execute plan to meet recruitment goals

CY15/16 Goals – Recruit Subjects & Perform Galvanic Stimulation

- ☐ Screen 140 subjects using vestibular and balance testing to characterize the vestibular impairments of Veteran with GWI
- ☐ Use of stochastic electrical stimulation in 42 GWI Veterans with vestibular impairments
- ☐ Analyze collected data and evaluate effectiveness of sub-sensory galvanic stimulation